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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,807	10/19/2001	Li Gan	019488-000711US	9177

24353 7590 01/24/2003

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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/24/2003 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/027,807	Gan
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 10/19/01, 4/11/02, 5/28/02, 11/25/02 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-51 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-51 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on Oct 19, 2001 is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☒ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 3, 17, 23- 36, and 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "a part of the candidate gene" in claims 3 and 23 is a relative term which renders the claims indefinite. The term "a part of the candidate gene" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The part of a gene may include a single nucleotide and therefore the claims are vague and indefinite.

The term "a portion of a gene" in claim 17 is a relative term which renders the claim indefinite. The term "a portion of a gene" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The portion of a gene may include a single nucleotide and therefore the claims are vague.

Regarding claim 51, the phrase "can be" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

4. Claims 1-4, 14-18, 23-26, 30, 33, 34, 35, 36, 38, 39, 41, and 48-50 are rejected under 35 U.S.C. 102(e) as being anticipated by Leptin (U.S. Patent 6,135,942) (October 24, 2000).

Leptin teaches a method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell (Abstract), the method comprising:

a) producing a plurality of cDNA, wherein each cDNA comprises at least a portion of a gene that is expressed in a cell (Example);

b) producing a candidate dsRNA from at least one of the cDNA (Figures 4A and 4B and Column 43, lines 25-35);

c) introducing the candidate dsRNA into a reference cell (Column 43, lines 41-43); and

d) identifying an active dsRNA by determining whether the candidate dsRNA modulates a desired candidate gene expression in the reference cell (Column 43, lines 43-45).

Leptin teaches a method, wherein the step of identifying the active dsRNA comprises:

a) selecting a candidate gene, wherein the candidate gene is a gene that is expressed in a test cell and/or a control cell, and/or is expressed at a detectably different level with respect to the test cell and the control cell, and the test cell and the control cell differ with respect to a cellular characteristic (Column 43, line 46 to Column 44, line 34); and

b) identifying whether the candidate dsRNA is an active dsRNA by determining whether down-regulation of expression of the candidate gene in a reference cell has a functional effect in the reference cell, wherein the determining comprises:

I) introducing the candidate dsRNA which is substantially identical to at least a part of the candidate gene into the reference cell (Column 43, lines 41 to Column 44, line 7); and

ii) detecting an alteration in a cellular activity or a cellular state in the reference cell, alteration indicating that the candidate gene plays a functional role in the reference cell and is an active dsRNA (Column 43, lines 43-45).

Leptin teaches a method, wherein the step of producing a plurality of cDNA comprises:

I) isolating at least one mRNA from the cell (Example and Column 43, lines 59-61), and

ii) producing a double-stranded cDNA from the isolated mRNA by reverse transcription (Example).

Leptin teaches a method for identifying and validating the effect of an active dsRNA which attenuates a desired gene expression in a cell (Example and Claims 8-9 and Column 46, line 6 to Column 47, line 46) and also a method for correlating genes and gene function, the method comprising:

a) producing a candidate dsRNA which comprises at least a portion of a candidate gene that is expressed in a control cell (Column 43, lines 41 to Column 44, line 7);

b) introducing the candidate dsRNA into a reference cell (Column 43, lines 41 to Column 44, line 7); and

c) identifying whether the candidate dsRNA is an active dsRNA by detecting an alteration in a cellular activity or a cellular state in the reference cell, alteration indicating that the candidate gene plays a functional role in the reference cell and is an active dsRNA (Example).

Leptin teaches a method, wherein the plurality of cDNA is produced from a plurality of mRNAs which are produced by the control cell (Example).

Leptin teaches a method, wherein the step of producing the plurality of candidate dsRNA comprises:

a) selecting a candidate gene, wherein the candidate gene is a gene that is expressed in a test cell and/or a control cell, and/or is expressed at a detectably different level with respect to the test cell and the control cell, and the test cell and the control cell differ with respect to a cellular characteristic (Example); and

b) producing the plurality of candidate dsRNAs, wherein each candidate dsRNA is substantially identical to at least a part of the candidate gene (Example).

Leptin teaches a method, wherein the candidate gene is selected from a normalized library prepared from cells of the same type as the test cell or the control cell and is present in low abundance in the normalized library. (Example)

Leptin teaches a method, wherein the candidate gene is a differentially expressed gene selected from a subtracted library that is enriched for genes that are differentially expressed with respect to the test cell and the control cell (Column 43, line 13 to Column 44, line 34).

Leptin teaches a method, wherein the subtracted library is also normalized and the candidate gene is one of the genes that is both present in low abundance and differentially expressed in the subtracted and normalized library (Example).

Leptin teaches a method, wherein the cellular characteristic is cell health, the test cell is diseased cell and the control cell is a healthy cell, and the candidate gene is potentially correlated with a disease (Column 41, line 33 to Column 44, line 34 and Example).

Leptin teaches a method, wherein the cellular characteristic is stage of development and the test cell and the control cell are at different stages of development, and the candidate gene is potentially correlated with mediating the change between the different stages of development (Example and Column 48, lines 56-62).

Leptin teaches a method, wherein the cellular characteristic is cellular differentiation and the candidate gene is potentially correlated with controlling cellular differentiation (Column 47, line 56 to Column 48, line 11).

Leptin teaches a method, wherein the candidate gene is an endogenous gene of the reference cell (Column 66, line 20 to Column 67, line 58).

Leptin teaches a method, wherein the candidate gene is present in the reference cell as an extrachromosomal gene (Example).

Leptin teaches a method, wherein the reference cell is part of a tissue of an organism (Column 48, lines 12-62)

Leptin teaches a method, wherein the reference cell is a mammalian cell (Column 35, lines 4-32).

Leptin teaches a method, wherein the reference cell is part of an organism and the detecting step comprises detecting a change in phenotype (Column 47, line 56 to Column 48, line 11).

Leptin teaches a method, wherein the determining step comprises determining whether interference with expression of the candidate gene in the reference cell is correlated with alteration of acellular activity or cellular state (Column 47, line 56 to Column 48, line 11).

Leptin teaches a method, wherein interference is achieved by introducing a double-stranded RNA into the reference cell that can specifically hybridize to the candidate gene (Example and Column 43, line 66 to Column 44, line 7).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 5-13, 19-21, and 37 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Petryshyn (U.S. Patent 6,124,091) (September 26, 2001).

Leptin teaches a method of claims 1-4, 14-18, 23-26, 30, 33, 34, 35, 36, 38, 39, 41, and 48-50 as described above.

Leptin does not teach a method, wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme.

Petryshyn teaches a method, wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme (Figure 2A and Example 1).

Leptin does not teach a method, wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA, and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment.

Petryshyn teaches a method, wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA (Example 1), and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment (Examples 1 and 4)

Leptin does not teach a method, wherein the plurality of cDNA comprises at least a portion of substantially all genes that are actively expressed in the cell.

Petryshyn teaches a method, wherein the plurality of cDNA comprises at least a portion of substantially all genes that are actively expressed in the cell (Example 1)

Leptin does not teach a method, wherein the desired effect of the candidate dsRNA on the reference cell is a result of the candidate dsRNA attenuating expression of a candidate gene in the reference cell.

Petryshyn teaches a method, wherein the desired effect of the candidate dsRNA on the reference cell is a result of the candidate dsRNA attenuating expression of a candidate gene in the reference cell (Example 1).

Leptin does not teach a method, wherein the candidate dsRNA has complete sequence identity with the candidate gene over at least 500 nucleotides and in between 500 and 1100 nucleotides in length.

Petryshyn teaches a method, wherein the candidate dsRNA has complete sequence identity with the candidate gene over at least 500 nucleotides and in between 500 and 1100 nucleotides in length (Column 3, lines 7-10).

Leptin does not teach a method wherein the reference cell is part of a cell culture.

Petryshyn teaches a method wherein the reference cell is part of a cell culture (Abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme.

wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA, and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment. of Petryshyn in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin since Petryshyn states, "A method of

inhibiting cell proliferation in bone marrow cells obtained from a patient suffering from a hematological cancer is also provided by the present invention (Column 5, lines 34-36)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme ( ).

wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA, and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment. of Petryshyn in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in order to achieve the express advantages, as noted by Petryshyn, of an invention which provides a method of inhibiting cell proliferation in bone marrow cells obtained from a patient suffering from a hematological cancer.

7. Claim 22 is rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Petryshyn (U.S. Patent 6,124,091) (September 26, 2001) further in view of kreitman et al. (U.S. Patent 6,027,876) (February 22, 2000).

Leptin in view of Petryshyn teach the method of claims 1-28, 23-26, 30, 33, 34-39, 41, and 48-50 as described above.

Leptin in view of Petryshyn do not teach the method wherein the restriction enzyme is Rsa1.

kreitman et al. teach the method wherein the restriction enzyme is Rsa1 (Figure 2 and Column 7, lines 16-22).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the restriction enzyme is Rsa of kreitman et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Petryshyn since kreitman et al. states, "Any restriction enzyme which produces a detectable polymorphism can be used. Preferably, the enzyme used will be a 4-cutter, such as Sau96I, RsaI (Column 7, lines 18-21)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the restriction enzyme is Rsa of kreitman et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Petryshyn in order to achieve the express advantages, as noted by kreitman et al., of a restriction enzyme which produces a detectable polymorphism which is preferably a 4-cutter, such as Sau96I, RsaI.

8. Claims 27-29 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Villeponteau et al. (U.S. Patent 6,300,110 B1) (October 9, 2001).

Leptin teaches the method of claims 1-4, 14-18, 23-26, 30, 33, 34, 35, 36, 38, 39, 41, and 48-50 as described above.

Leptin does not teach the method wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified.

Villeponteau et al. teach the method wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified.(Column 33, line 19 to column 34, line 42).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified of Villeponteau et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin since Villeponteau et al. states, "The resultant recovered product species (typically an expressed sequence tag or EST cDNA) can be subcloned into a replicable vector with or without attachment of linkers, amplified further, and/or sequenced directly. Once the EST is recovered, it can be used to obtain a substantially full length cDNA from a cDNA library (Column 34, lines 43-48)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified of Villeponteau et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in order to achieve the express advantages, as noted by Villeponteau et al, of a method which can be used to obtain a substantially full length cDNA from a cDNA library.

9. Claims 31, 32, 40, and 42-44 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000).

Leptin teaches the method of claims 1-4, 14-18, 23-26, 30, 33, 34, 35, 36, 38, 39, 41, and 48-50 as described above.

Leptin does not teach the method wherein the test cell is obtained from a mammal that has had a stroke or neurological disease.

Der et al teaches the method wherein the test cell is obtained from a mammal that has had a stroke or neurological disease (Column 19, lines 1-20 and Column 19, line 63 to Column 20, line 9).

Leptin does not teach the method wherein the reference cell is part of an embryo.

Der et al teaches the method wherein the reference cell is part of an embryo (Column 20, lines 20-40).

Leptin does not teach the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell.

Der et al teaches the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell. (Column 19, lines 1-20).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell or embryo of Der et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin since Der et al. states, "The activity of the substances, antibodies, antisense nucleic acid molecules, and composition of the invention may be confirmed in animal experimental model systems. For example, models of peripheral nervous system damage include animals having damaged axons, such as axotomized facial neurons, models of neurodegenerative conditions include the MPTP model, and models of traumatic and non-traumatic peripheral nerve damage include animal stroke (Column 19, line 63 to column 20, line 9)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell or embryo of Der et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in order to achieve the express advantages, as noted by Der et al., of animal experimental model systems in which the

activity of the substances, antibodies, antisense nucleic acid molecules, and composition of the invention may be confirmed.

10. Claims 45-47 and 51 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000) further in view of Staddon et al. (U.S. Patent 6,312,686 B1) (November 6, 2001).

Leptin in view of Der et al teach the method of claims 1-4, 14-18, 23-26, 30-36, 38-44, and 48-50 as described above.

Leptin in view of Der et al do not teach the method, wherein the reference cell has increased sensitivity to N-methyl-D-aspartate and the detecting step comprises detecting a decrease in cellular sensitivity to N-methyl-D-aspartate.

Staddon et al. teach the method, wherein the reference cell has increased sensitivity to N-methyl-D-aspartate and the detecting step comprises detecting a decrease in cellular sensitivity to N-methyl-D-aspartate (Column 14, lines 7-67).

Leptin in view of Der et al do not teach the method, wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the candidate gene binds to another protein to form a complex that can be coimmunoprecipitated.

Staddon et al. teach the method, wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the

candidate gene binds to another protein to form a complex that can be coimmunoprecipitated (Figures 12-16 and Column 17, lines 5-37).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the candidate gene binds to another protein to form a complex that can be coimmunoprecipitated of Staddon et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al since Staddon et al. states, "The invention therefore has use in a method of reducing permeability of a physiological barrier such as the blood-brain barrier, the method comprising administering to a subject an effective amount of an agent which promotes tyrosine protein dephosphorylation (Column 3, lines 20-24)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the candidate gene binds to another protein to form a complex that can be coimmunoprecipitated of Staddon et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al in order to achieve the express advantages, as noted by Staddon et al., of an invention which has use in a method of reducing permeability of a physiological barrier such as the blood-brain barrier,

method comprising administering to a subject an effective amount of an agent which promotes tyrosine protein dephosphorylation.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

January 14, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600